During the war I took part in making the atomic bomb. When the war was ending, I, like many others, cast around for a new field of research. Partly on account of the bomb, I had lost some interest in physics. I was therefore very interested when I read Schrödinger's book "What is Life" and was struck by the concept of a highly complex molecular structure which controlled living processes. Research on such matters seemed more ambitious than solid-state physics. At that time many leading physicists such as Massey, Oliphant, and Randall (and later I learned that Bohr shared their view) believed that physics would contribute significantly to biology; their advice encouraged me to move into biology.

I went to work in the Physics Department at St. Andrews, Scotland, where Randall had invited me to join a biophysics project he had begun. Stimulated by Muller's experimental modification, by means of X-radiation, of genetic substance, I thought it might be interesting to investigate the effects of ultrasonics; but the results were not very encouraging.

The biophysics work then moved to King's College, London, where Randall took the Wheatstone Chair of Physics and built up, with the help of the Medical Research Council, an unusual laboratory for a Physics Department, where biologists, biochemists and others worked with the physicists. He suggested I might take over some ultra-violet microscope studies of the quantities of nucleic acids in cells. This work followed that of Caspersson, but made use of the achromatism of reflecting microscopes. By this time, the work of Caspersson (1941) and Brachet (1941) had made the scientific world generally aware that nucleic acids had important biological roles which were connected with protein synthesis. The idea that DNA might itself be the genetic substance was, however, barely hinted at. Its function in chromosomes was supposed to be associated with replication of the protein chromosome thread. **The work of Avery, MacLeod and McCarty, showing that bacteria could be genetically transformed by DNA, was published in 1944, but even in 1946 [illegible] almost unknown, or if known its significance was often belittled.**

It was fascinating to look through microscopes at chromosomes in cells, but I began to feel that as a physicist I might contribute more to biology by studying macromolecules isolated from cells. I was encouraged in this by Gerald Oster who came from Stanley's virus laboratory and interested me in particles of tobacco mosaic virus. As Caspersson had shown, ultra-violet microscopes could be used to find the orientation of ultra-violet absorbing groups in molecules as well as to measure quantities of nucleic

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acids in cells. Bill Seeds and I studied DNA, proteins, tobacco mosaic virus, vitamin B12, etc. While examining oriented films of DNA prepared for ultraviolet dichroism studies, I saw in the polarising microscope extremely uniform fibres giving clear extinction between crossed nicols. I found the fibres had been produced unwittingly while I was manipulating DNA gel. Each time that I touched the gel with a glass rod and removed the rod, a thin and almost invisible fibre of DNA was drawn out like a filament of spider's web. The perfection and uniformity of the fibres suggested that the molecules in them were regularly arranged. I immediately thought the fibres might be excellent objects to study by X-ray diffraction analysis. I took them to Raymond Gosling, who had our only X-ray equipment (made from war-surplus radiography parts) and who was using it to obtain diffraction photographs from heads of ram spermatozoa. This research was directed by Randall, who had been trained under W. L. Bragg and had worked with X-ray diffraction. Almost immediately, Gosling obtained very encouraging diffraction patterns (see fig. 1). One reason for this success was that we kept the fibres moist. We remembered that, to obtain detailed X-ray patterns from proteins, Bernal had kept protein crystals in their mother liquor. It seemed likely that the configuration of all kinds of water-soluble biological macromolecules would depend on their aqueous environment. We obtained good diffraction patterns with DNA made by Signer and Schwander (1949), which Signer brought to London to a Faraday Society meeting on nucleic acids and which he generously distributed so that all workers, using their various techniques, could study it.

Realisation that the genetic material was a pure chemical substance, and signs that its molecular structure was singularly simple

Between 1946 and 1950 many lines of evidence were uncovered indicating that the genetic substance was DNA, not protein or nucleoprotein. For instance, it was found that the DNA content of a set of chromosomes was constant, and that DNA from a given species had a constant composition although the nucleotide sequence in DNA molecules was complex. It was suggested that genetic information was carried in the polynucleotide chain in a complicated sequence of the four nucleotides. The great significance of bacterial transformation now became generally recognised, and the

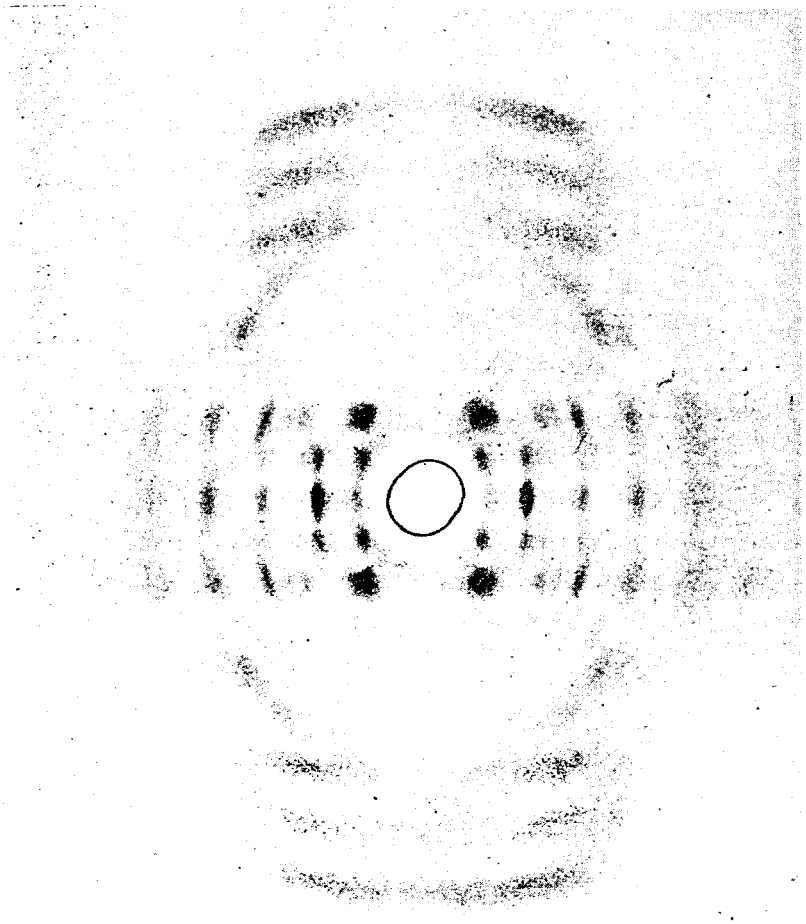

Fig. 1. One of the first X-ray diffraction photographs of DNA taken in our laboratory. This may be compared with the later photograph in Fig. 9. (photograph with R. Gosling; DNA by R. Signer).

demonstration by Hershey and Chase (1952) that bacteriophage DNA carried the viral genetic information from parent to progeny helped to complete what was a fairly considerable revolution in thought.

The prospects of elucidating genetic function in terms of molecular structure were greatly improved when it was known that the genetic substance was DNA, which had a well defined chemical structure, rather than an ill-defined nucleoprotein. There were many indications of sim-

plicity and regularity in DNA structure. The chemists had shown that DNA was a polymer in which the phosphate and deoxyribose parts of the molecule were regularly repeated in a polynucleotide chain with 3'—5' linkages. Chargaff (1950) discovered an important regularity: although the sequence of bases along the polynucleotide chains was complex and the base composition of different DNA's varied considerably, the numbers of adenine and thymine groups were always equal, and so were the numbers of guanine and cytosine. In the electron microscope, DNA was seen as a uniform unbranched thread of diameter about 20 Å. Signer, Caspersson and Hammarsten (1938) showed by flow-birefringence measurements that the bases in DNA lay with their planes roughly perpendicular to the length of the thread-like molecule. Their ultra-violet dichroism measurements gave the same results and showed marked parallelism of the bases in the DNA in heads of spermatozoa. Earlier Schmidt (1937) and Pattri (1932) had studied optically the remarkable ordering of the genetic material in sperm heads. Astbury (1947) made pioneer X-ray diffraction studies of DNA fibres and found evidence of considerable regularity in DNA; he correctly interpreted the strong 3.4 Å reflection as being due to planar bases stacked on each other. The electro-titrometric study by Gulland and Jordan (1947) showed that the bases were hydrogen-bonded together, and indeed Gulland (1947) suggested that the polynucleotide chains might be linked by these hydrogen bonds to form multi-chain micelles.

Thus the remarkable conclusion that a pure chemical substance was invested with a deeply significant biological activity coincided with a considerable growth of many-sided knowledge of the nature of the substance. Meanwhile we began to obtain detailed X-ray diffraction data from DNA. This was the only type of data that could provide an adequate description of the 3-dimensional configuration of the molecule.

The need for combining X-ray diffraction studies of DNA with molecular model-building

As soon as good diffraction patterns were obtained from fibres of DNA, great interest was aroused. In our laboratory, Alex Stokes provided a theory of diffraction from helical DNA. Rosalind Franklin (who died some years later at the peak of her career) made very valuable contributions to the X-ray analysis. In Cambridge, at the Medical Research Council laboratory